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An inhalation distribution model for the lactating mother and nursing child

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SUMMARY

A rule-of-thumb methodology is presented to assist in assessing risk to a nursing child due to the mother's occupational inhalation exposure. The method represents an example of the use of physiologically based pharmacokinetic modeling using state-of-the-art computational techniques. A computer model is developed to describe distribution of non-metabolized, inhaled contaminants into a mother/child system as a function of the contaminant's blood:air and octanol:water partition coefficients. Risk is assessed in terms of the area under the blood concentration vs. time curve of the exposure chemical. Since low partition values yield low risk for the nursing child and high values yield high risk, the model is exercised over a range of intermediate values (blood:air = [2,25]; octanol:water = [100, 1500]). Results are thus applicable to chemicals for which the mother's dose is a strong factor in estimating the child's risk. The most notable observation is that, for the range of partition values used, this model never predicts a risk for the child greater than 25% of that of the mother. An equation is provided (based on model results) that expresses the child's risk as a fraction of the mother's risk.

INTRODUCTION

The increasing number of women in the workplace has raised new issues in the area of safe workplace exposure criteria. One such issue involves workplace exposure of the lactating mother and risk to the nursing child due to chemicals in the milk. Uncertainties involve more than simply the possibility of increased sensitivity

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in the newborn. Quantifying the infant's exposure from the mother's breathing zone air concentration involves a chemical distribution and transport description employing physiological parameters that are sparsely represented in the literature. Occupational physicians often feel compelled to recommend removal of the nursing mother from the work environment due to lack of data concerning risk to the child. The present work employs mathematical simulation to describe the distribution of a chemical from the mother's breathing zone during a work shift to a child on a 24-h nursing schedule. The purpose is to elucidate trends in distribution to the child based on physicochemical characteristics of the exposure chemical (i.e., partition coefficients into tissues). The chemical's metabolism is not included in this preliminary model.

MATERIALS AND METHODS

Model description

A system of mass balance equations was constructed using the conceptual model shown in Fig. 1. Physiologically based toxicokinetic principles were employed using realistic ventilation rates, tissue volumes, and blood flows to tissue groups, as well as estimated rates of milk production and partitioning of chemical to milk. A chemical enters the system by alveolar equilibration with blood flow in the mother during a work shift and exits by both mother and child exhalation. The child receives a chemical dose by direct transfer of bulk milk from the mother's mammary compartment to the child's gastrointestinal (GI) tract according to the nursing schedule and the concentration in the mother's milk compartment at the time of nursing. GI absorption of chemical by the infant is assumed to be instantaneous with a bioavailability of 1.0. Risk is expressed in terms of the area under the blood concentration vs. time curve (AUCB), which is analogous to an effective dose at a given point in time (an index of potential to express a toxic effect). Thus, the child's risk

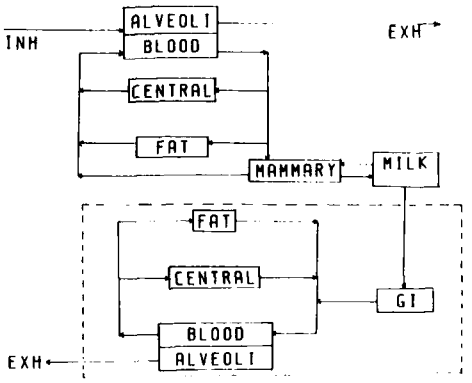

Fig. 1. Conceptual model of a mother/nursing child distribution system.

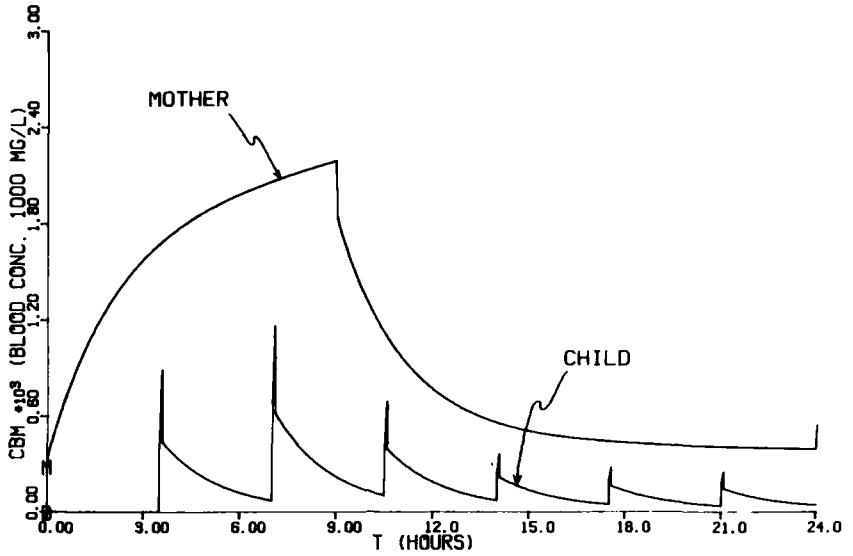

Fig. 2. Blood concentration vs. time curve for 9-h workshift and 3.5 h nursing schedule. ($P_{B:A} = 25$; $P_{O:W} = 1500$).

may be stated in terms of a fraction of the mother's risk (whatever the mother's risk may be for a particular chemical). That is, the relative risk to the child (RRC) is expressed by the following equation:

RRC = AUCB (child)/AUCB (mother)

Fig. 2 shows the model predictions of AUCB for mother and child illustrating a 9-h work shift and a 3.5-h nursing schedule. An RRC value of 0.5 would indicate that the child's risk is one-half that of the mother's for the described exposure and nursing scenario. Loss of chemical by metabolism and urinary excretion depends on specific metabolic pathways and thus is not included in this generic distribution model. Consequently, transfer of a toxic metabolite from the mother to the child is not described. However, in the case of short-lived, reactive metabolites, this potential for toxicity in either the mother or the child should be proportional to the AUCB for each.

Using the model described above, the child's risk relative to the mother's risk is expressed under the following critical assumptions.

1) The mother's exposure is by inhalation only.
2) Distribution is described sufficiently by considering central and fat tissue groups and a third mammary/milk compartment in the mother.
3) Absorption of chemical in the child's GI tract is 100%.
4) Loss of chemical by metabolism and urinary excretion is neglected in both mother and child.

5) The child's relative risk is represented accurately by the ratio of child's to mother's AUCB.

The blood:air partition coefficient is entered directly into the model. Fat:blood and milk:blood partition coefficients are calculated from the more common octanol:water partition coefficient according to the following expressions:

$$P_{\text{fat:blood}} = 70.9 \log (P_{\text{oct:water}}) - 127.0$$

$$P_{\text{milk:blood}} = 0.04\ P_{\text{fat:blood}} + 0.96\ (1.0)$$

The first equation is derived empirically from literature partition coefficient data [1–3]. The second equation is based on the assumption of 4% fat content in human milk. The model thus exercises a defined exposure/nursing scenario with input values of blood:air and octanol:water partition coefficients. Ranges of values used in the model were $P_{B:A}$ (2,25) and $P_{O:W}$ (100, 1500). These values are typical of organic chemicals of inhalation concern in the workplace. Low $P_{O:W}$ chemicals do not readily distribute to adipose tissue and are fairly quickly eliminated, presenting little hazard to the child. High $P_{O:W}$ chemicals are stored readily in adipose tissue and partition easily to milk, resulting in long-term release from tissue and distribution to the child for high infant risk [4]. The values used in this model are intermediate in range and thus represent chemicals for which the mother's dose is a strong factor in estimating the child's risk. Simulation was performed using Advance Continuous Simulation Language (ACSL) by Mitchell and Gauthier, and Statistical Analysis System (SAS) was used for the plotting and curve fitting of model results.

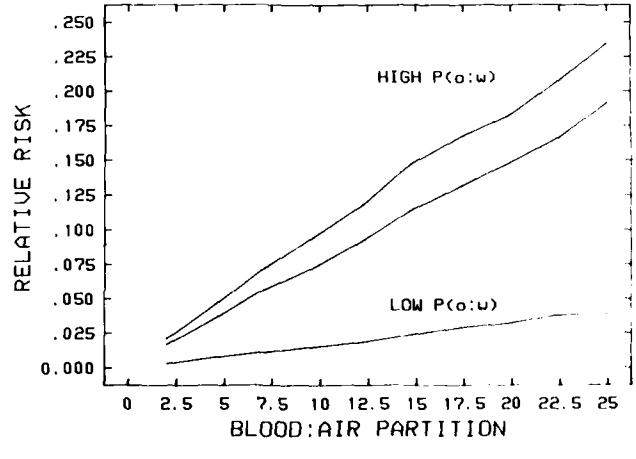

Fig. 3. Child's relative risk (compared to mother's risk) vs. blood:air partition coefficient for $P_{O:W}$ values of 100, 722, and 1500.

RESULTS AND DISCUSSION

The results demonstrate a clear upward trend in RRC with increasing values of $P_{B:A}$ and $P_{O:W}$, as illustrated in Figs. 3 and 4 which are plots of model results. Fig. 3 demonstrates a linear relationship of child's relative risk to the blood:air partition coefficient. This is easily explained since $P_{B:A}$ directly controls the rate of the child's elimination by exhalation. The effect of $P_{O:W}$, as shown in Fig. 4, is not as straightforward since it controls the amount of chemical distributed to milk and the amount distributed to the child's fat tissue and subsequently released back into distribution. The most notable observation is that for the range of partition values used, this model never predicts a risk for the child greater than 25% of that of the mother.

Sensitivity analyses were performed to determine physiological factors that significantly influenced model results. The duration of a single nursing had little effect until the duration was reduced to 5 min. Since most of the milk volume is, in fact, taken up early in a nursing session, 5 min was used as the nursing duration in the model. Blood flow to the child's fat tissue demonstrated a definite inverse relationship to the child's risk, particularly in the case of high $P_{O:W}$. The value used in the model was approximately one-half that estimated in the literature to influence model results toward the conservative side. Both the volume of milk per feeding and the fat content of the milk are directly related to the child's risk. The literature value of 4% milk-fat was used since variation from human to human should be small. Milk volume per feeding was double that of the literature average value to conservatively account for variation. All other physiological factors which were com-

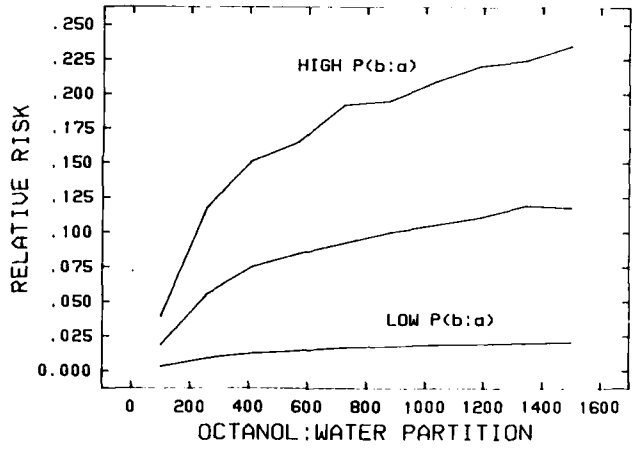

Fig. 4. Child's relative risk (compared to mother's risk) vs. octanol:water partition coefficient for $P_{B:A}$ values of 2, 12, and 25.

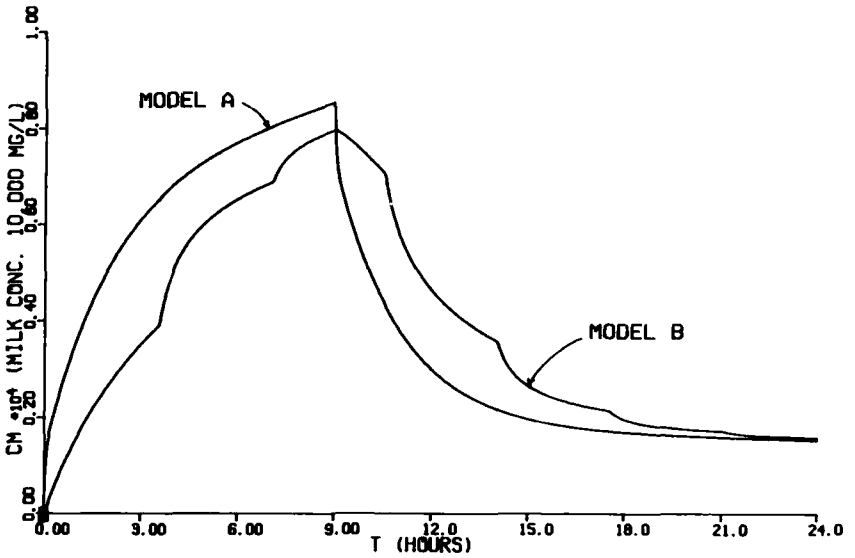

Fig. 5. Milk concentration vs. time curve for two separate models describing alternative mechanisms for the loading of chemical into milk: (1) continual equilibration with mammary blood flow (model A); and (2) accumulation according to mammary tissue concentration at the time of incremental milk production (model B).

ponents of the model did not significantly influence model results when varied over a reasonable range.

Of particular concern was the model description of chemical loading of the mother's milk compartment. Transport mechanisms between mammary tissue and bulk milk are not clearly established in the literature. Therefore, two separate models were exercised: (1) model 'A' which controlled milk concentration by continual equilibration with mammary blood flow, and (2) model 'B' which accumulated chemical in the milk based on mammary tissue concentration at the time of milk production. In the latter case, milk concentration reflects the mother's history of blood concentration rather than current blood concentration and thus always lags behind milk concentration predicted by the former model. That is, during the mother's work exposure, milk concentration is lower than in the former model and higher after exposure, as illustrated in Fig. 5. Results from each model were essentially the same, apparently due to this compensation effect.

Finally, the effect of altering the mother's work schedule was studied. Results showed that increasing the work shift from 8 to 12 h increased the child's relative risk by only 0.1. However, after only one shift exposure, the child's relative risk continued to rise days after the single exposure. This is due to a gradual releasing of stored chemical from the mother to a child having a much smaller volume of distribution. Thus, chemical accumulation over multiple workshifts is suggested.

Employing daily workshifts and exercising the model over an extended period, it was shown that the child's relative risk increased and approached an asymptotic value, 90% of that value being reached in approximately 2 months. Therefore, the model used to generate the final results shown in Figs. 3 and 4 employs a continuous 9-h work shift, 7 days/week, for 2 months. The child nurses every 3.5 h.

To interpret these findings in terms of guidelines for potential field use, an equation was derived empirically from model results, expressing the child's relative risk in terms of the chemical's blood:air and octanol:water partition coefficients as follows:

$$\mathrm{RRC} = 2.5 \times 10^{-4} P_{\mathrm{B:A}} \sqrt{P_{\mathrm{O:W}}}$$

The equation is, of course, limited to the range of values and model assumptions specified above.

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